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ORIGINAL ARTICLE

Prophylactic Effectiveness of Suplatast Tosilate in Children with Asthma Symptoms in the Autumn: A Pilot Study

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ABSTRACT

Background: Exacerbations of bronchial asthma usually occur in the autumn. To our knowledge, however, the effectiveness of drugs for preventing exacerbations of asthma in the autumn has not been studied previously, except for leukotriene receptor antagonists and Omalizmab.

Methods: This study compared the prophylactic effectiveness of suplatast tosilate with that of mequitazine in children with asthma symptoms, which is usually exacerbated in the autumn. The study group comprised 27 children aged 2 to 15 years who required treatment for asthmatic attacks during the past year and tested positive at least for mite allergen in the preceding autumn. The subjects were randomly assigned to receive either suplatast or mequitazine. The primary endpoint of this study was the number of days without symptoms during the 8 weeks of treatment. In addition, the Japanese Pediatric Asthma Control Program (JPAC) scores were also recorded every 2 weeks in each group.

Results: Overall, 14 patients received suplatast, and 13 received mequitazine for 8 weeks from September through early October. During follow-up, the number of days without symptoms and the total JPAC scores did not differ significantly between the groups. However, as compared with weeks 1 to 2 of treatment, the mean number of days without symptoms during weeks 7 to 8 increased significantly in only the suplatast group (8.6 vs. 11.5 days; $p = 0.004$).

Conclusions: Our results suggest that short-term additional treatment with suplatast is useful for preventing asthma symptoms in children with asthma, which is usually exacerbated in the autumn.

KEY WORDS

asthma, pediatrics, seasonal, suplatast tosilate, Th2 cytokines

INTRODUCTION

Exacerbations of bronchial asthma usually occur in the autumn.[1-4] One of the reasons why asthma is exacerbated is that autumn is also viral season which leads to major exacerbations of asthma. Leukotriene receptor antagonists have been reported to prevent exacerbations of asthma associated with airway infections in the autumn.[5] Omalizmab is also shown to prevent seasonal exacerbations.[6] To our knowledge, however, the effectiveness of other types of drugs for preventing exacerbations of asthma in the autumn has not been studied previously. It is suggested that suplatast tosilate is effective for antileukotriene nonresponders with asthma.[7] One of the reasons of why suplatast tosilate is effective for antileukotriene nonresponders is relationship between the benefits of suplatast tosilate and gene polymorphisms.[8,9] Therefore, it becomes a useful option if suplatast tosilate is effective in preventing exacerbation of asthma in the

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autumn. So, we compared the additive effectiveness of suplatast with that of mequitazine for the prevention of exacerbations of asthma in the autumn.

METHODS

This study is an open label, multicenter, randomized Phase II study investigating prophylactic effectiveness of suplatast tosilate with that of mequitazine in children with asthma, which is usually exacerbated in the autumn. As previously noted, because of the potentially effect of suplatast tosilate on antileukotriene non-responders, current study compared mequitazine with suplatast tosilate, without comparing leukotriene receptor antagonists, to establish its prophylactic effect on asthma exacerbated in the autumn. Suplatast tosilate is thought to act by inhibiting cytokine production by type 2 helper T (Th2) cells and improving the balance between type 1 helper T (Th1) cells and Th2 cells, thereby exerting antiallergic effects.[10,11] On the other hand, mequitazine is a histamine H1 receptor antagonist (H1RA). Although H1RA doesn't have sufficient evidence for effectiveness against asthma, it has been approved in Japan as a medicine for pediatric asthma. So we used mequitazine as a control to investigate the effect of Suplatast tosilate.

STUDY DESIGN

Children 2 to 15 years of age with bronchial asthma were eligible in this multicenter, collaborative, controlled clinical trial from September 1, 2009 through December 31, 2009. Asthma diagnosis is based on the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2008 (JPGL2008). Disease severity of the subjects consisted of mild persistent and moderate persistent type, mild intermittent and severe persistent type were excluded. All subjects required rescue inhaled β_2 stimulator to manage asthmatic attacks during the past year and had missed at least 1 day of school because of asthma during the past year, or their daily activities were markedly restricted. Patients had a history of asthmatic attacks in the autumn of the previous year and tested positive at least for mite allergen (capsulated hydrophilic carrier polymer radioallergosorbent tests). Informed consent to participate in the study was obtained from the parents or guardians of 27 children with asthma. The subjects were randomly assigned to receive either suplatast (14 patients) or mequitazine (13 patients). In the suplatast group, patients received suplatast tosilate dry syrup (6 mg/kg/day). In the mequitazine group, patients received mequitazine (0.24 mg/kg/day) as pediatric syrup, pediatric fine granules, or tablets. These are approved dosages in Japan. In each group, suplatast or mequitazine was administered in addition to the patients' usual antiasthmatic medications for 8 weeks to assess the prophylactic effect on symptoms. The numbers of days without symptoms and the Japanese Pediatric Asthma Control Program (JPAC) scores were recorded every 2 weeks in each group. The primary endpoint was the number of days without symptoms during the 8 weeks of treatment. The prophylactic effect on asthmatic symptoms was also compared between the groups.

STATISTICAL ANALYSIS

The primary end point was the number of days without signs or symptoms of asthma (no asthmatic symptoms, no sleep disturbances at night, and no treatment with relievers) according to the patient's asthma diary. The statistical significance of differences between the suplatast group and mequitazine group in the numbers of days without asthmatic symptoms, JPAC scores for each variable evaluated, and total JPAC scores was evaluated with two-sample t-tests. Treatment effectiveness over time in each group was compared with the use of paired t-tests.

ETHICS

This study was approved by the Regional Ethics Committee for Human Research at Dokkyo Medical University Hospital. Oral and written informed consent was obtained from the parents or guardians of all patients participating in this study.

JPAC SCORES

JPAC scores are designed to facilitate the long-term management of asthma according to the Japanese Pediatric Guideline for the Treatment and Management of Asthma (JPGL), issued by the Japanese Society of Pediatric Allergy and Clinical Immunology.[12] The scores can be used to evaluate disease severity according to the JPGL. Patients and their guardians were interviewed to ascertain the following variables: 1) the severity of wheezing, 2) the number of dyspnea episodes, 3) the frequency of night awakening, 4) coughing and wheezing on exertion, and 5) the frequency of inhalant, oral medicine, or patch use for asthma exacerbation in the last month. Disease severity (intermittent type, mild persistent type, moderate persistent type, and severe persistent type) was evaluated on the basis of the severest symptom among interview variables 1) to 3) if the patient was not receiving long-term maintenance therapy. If the patient was already receiving long-term maintenance therapy, disease severity was evaluated on the basis of the treatment step and asthmatic symptoms during the past month. Control status was evaluated on the basis of the total scores for the 5 interview items, each of which was divided into 4 levels ranging from 0 to 3. The best status was assigned a score of 3, and the worst status was assigned a score of 0. A total score of 15 (3 points for each of the 5 interview items) was defined as complete control, a score 12 to 14 as good control, and a score of 11 or lower as poor control.

Table 1 Patient background

	Suplatast (n = 14)	Mequitadine (n = 13)	P value*
Age: mean (range)	5.9 (2-12)	6.3 (2-13)	0.732
Sex: male/female	10/4	10/3	0.745
Disease severity			0.310
mild persistent type	7	9	
moderate persistent type	7	4	
Usual antiasthmatic medication†			0.892
Patient using combination any drug	12 (86%)	11 (85%)	
Pranlukast hydrate	10 (71%)	6 (46%)	
Montelukast sodium	5 (36%)	5 (38%)	
Salmeterol xinafoate/fluticasone propionate combination inhaler	4 (29%)	3 (23%)	
Budesonide	4 (29%)	2 (15%)	
Sodium cromoglicate inhaler	1 (7%)	1 (8%)	
Fluticasone inhaler	1 (7%)	0 (0%)	
Beclomethasone (erosol)	1 (7%)	0 (0%)	
Oxatomide	1 (7%)	0 (0%)	

*P values for age were calculated with the use of the t-test. P values for sex, disease severity, and usual antiasthmatic medication were calculated with the use of the chi-square test.

†Total number of patients.

RESULTS

A total of 27 children were enrolled, and the prophylactic effectiveness against asthmatic symptoms was analyzed. The mean age of the subjects was 5.9 years (range; 2-12 years) in the suplatast group (14 patients) and 6.3 years (range; 2-12 years) in the mequitazine group (13 patients) (Table 1). Disease severity in the suplatast group was, mild persistent type in 7, and moderate persistent type in 7. In the mequitazine group, disease severity was mild persistent type in 9 patients and moderate persistent type in 4. There are not notable adverse event in the both groups. Usual antiasthmatic medications started since diagnosis of asthma was made. These usual medications were not changed during the treatment period.

The primary endpoint of this study was the number of days without symptoms during the 8 weeks of treatment. During follow-up, the mean number of days without symptoms during weeks 7 to 8 of treatment did not differ significantly between the suplatast group and the mequitazine group (11.5 days vs. 9.7 days; p = 0.378). However, as compared with weeks 1 to 2 of treatment, the mean number of days without symptoms during weeks 7 to 8 increased significantly in the suplatast group (8.6 vs. 11.5 days; p = 0.004), but did not change in the mequitazine group (9.5 vs. 9.7 days; p = 0.811) (Fig. 1). Similarly, JPAC scores during follow-up did not differ between the groups (mean total JPAC scores after 8 weeks of treatment, 14.3 points in the suplatast group vs. 13.2 points in the mequitazine group; p = 0.110) (Fig. 2). As compared with 4 weeks before treatment began, however, the mean total JPAC scores after 8 weeks of treatment increased significantly in only the suplatast group (suplatast group, 12.1 points vs. 14.3 points, p = 0.001; mequitazine group, 12.8 points vs. 13.2 points, p = 0.420). As for the effect of treatment on individual JPAC variables, the increase in the "coughing and wheezing on exertion" score after 8 weeks of treatment as compared with 4 weeks before treatment began was significantly greater in the suplatast group than in the mequitazine group (suplatast group, 2.9 points vs. mequitazine group, 2.5 points; p = 0.022) (Fig. 3). In addition, as compared with 4 weeks before treatment began, the mean "coughing and wheezing on exertion" score after 8 weeks of treatment increased significantly in only the suplatast group (suplatast group, 2.4 vs. 2.9 points, p = 0.006; mequitazine group, 2.4 vs. 2.5 points, p = 0.337).

DISCUSSION

On the basis of the number of days without symptoms and the JPAC scores, there was a trend toward greater improvement in the mequitazine group during the first 4 weeks of treatment (Fig. 2). Subsequently, however, symptoms improved considerably in the suplatast group, and at 8 weeks, the effectiveness of suplatast surpassed that of mequitazine. These findings suggest that about 1 month is required for suplatast to become effective. Therefore, when suplatast is used to prevent asthmatic attacks,

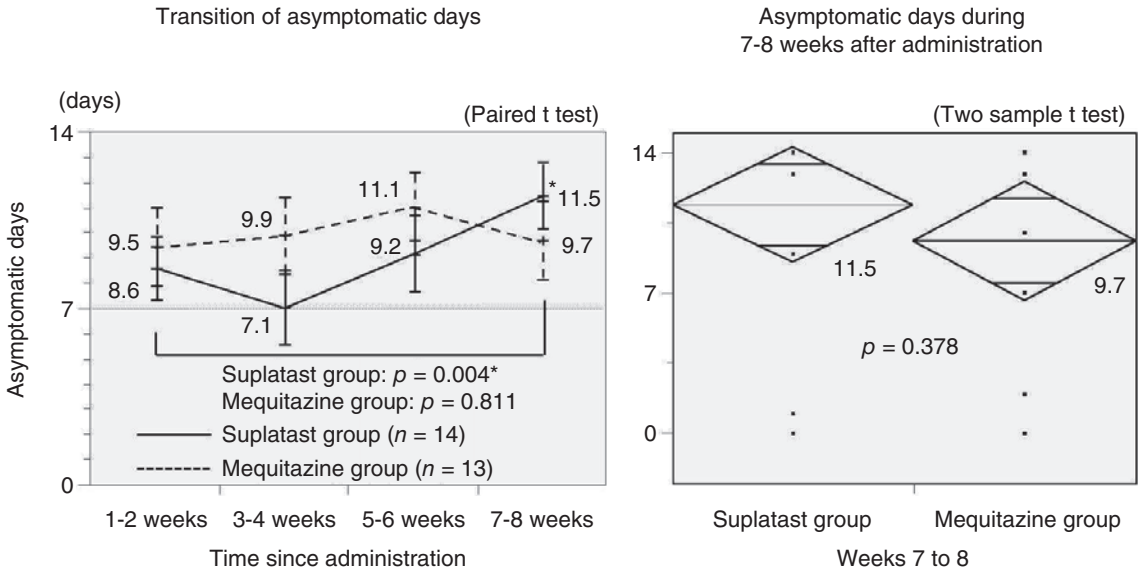

Fig. 1 Transition of asymptomatic days. The mean number of days without symptoms during weeks 7 to 8 of treatment did not differ significantly between the suplatast group and the mequitazine group. However, as compared with weeks 1 to 2 of treatment, the mean number of days without symptoms during weeks 7 to 8 increased significantly in the suplatast group, but did not change in the mequitazine group.

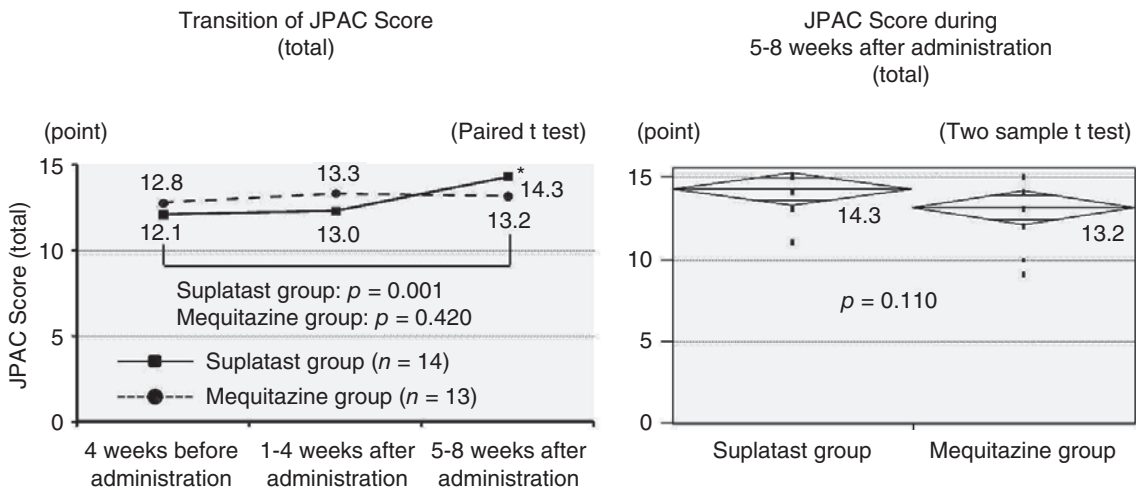

Fig. 2 Comparison of total JPAC score. As compared with 4 weeks before treatment began, the mean total JPAC score after 8 weeks of treatment increased significantly in only the suplatast group.

treatment should be started about 1 month before the beginning of autumn to ensure effective prophylaxis.

We previously reported the secondary prevention of asthma by suplatast in infants with atopic dermatitis caused by food allergies, considered a high risk factor for asthma.[13] Our results showed that suplatast significantly inhibited the onset of wheezing and the need for hospitalization due to wheezing, as compared with ketotifen fumarate. We found that suplatast had a secondary preventive effect on atopic asthma.

Exercise-induced asthma (EIA) has been linked to airway hyperresponsiveness and airway inflammation.[14] Suplatast can improve airway hyperresponsiveness and airway inflammation and alleviate asthmatic symptoms.[15] In our study, the improvement in coughing and wheezing on exertion was significantly greater in the suplatast group than in the mequitazine group. Suplatast may thus become an important treatment option for exercise-induced asthma in the future.

In our current study, children with asthma were enrolled in the autumn for only 4 months. Therefore, our study was not large. In addition, we evaluated re-

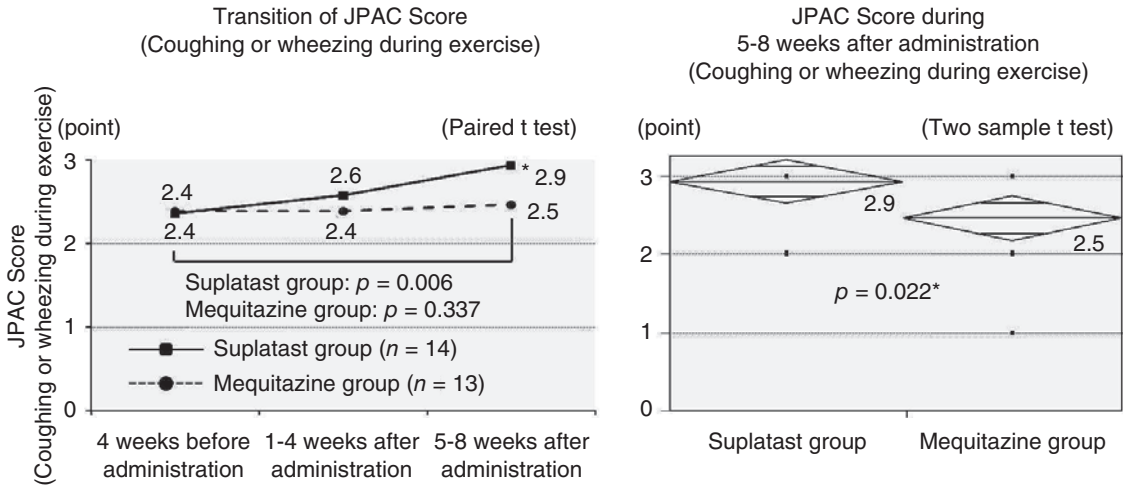

Fig. 3 Comparison of coughing and wheezing on exertion score. Mean "coughing and wheezing on exertion" score after 8 weeks of treatment increased significantly between the suplatast group and the mequitazine group. In addition, as compared with 4 weeks before treatment began, the mean score after 8 weeks of treatment increased significantly in only the suplatast group.

sponse during up to 8 weeks of treatment. Suplatast was shown to be effective after at least 4 weeks of treatment, but it is unclear whether the effect plateaued by week 8. Further larger studies are thus needed to determine whether long-term treatment with suplatast for more than 8 weeks is useful for preventing exacerbations of asthma.

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